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<p>(54) Title: IMPROVED VISION THROUGH PHOTODYNAMIC THERAPY OF THE EYE (57) Abstract  Photodynamic therapy of conditions of the eye, especially those conditions characterized by unwanted neovascularity, such as age-related macular degeneration, results in enhanced visual acuity for treated subjects.</p>		

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## IMPROVED VISION THROUGH PHOTODYNAMIC THERAPY OF THE EYE

### Technical Field

5           The invention relates to a method to improve visual acuity by administering photodynamic therapy (PDT) to the eye.

### Background Art

10           Loss of visual acuity is a common problem associated with aging and with various conditions of the eye. Particularly troublesome is the development of unwanted neovascularization in the cornea, retina or choroid. Choroidal neovascularization leads to hemorrhage and fibrosis, with resultant visual loss in a number of recognized eye diseases, including macular degeneration, ocular histoplasmosis syndrome, myopia, and inflammatory diseases. Age-related macular  
15           degeneration (AMD) is the leading cause of new blindness in the elderly, and choroidal neovascularization is responsible for 80% of the severe visual loss in patients with this disease. Although the natural history of the disease is eventual quiescence and regression of the neovascularization process, this usually occurs at the cost of sub-retinal fibrosis and vision loss.

20           Current treatment of AMD relies on occlusion of the blood vessels using laser photocoagulation. However, such treatment requires thermal destruction of the neovascular tissue, and is accompanied by full-thickness retinal damage, as well as damage to medium and large choroidal vessels. Further, the subject is left with an atrophic scar and visual scotoma. Moreover, recurrences are common, and visual  
25           prognosis is poor.

          Developing strategies have sought more selective closure of the blood vessels to preserve the overlying neurosensory retina. One such strategy is photodynamic therapy, which relies on low intensity light exposure of photosensitized tissues to produce deleterious effects. Photoactive compounds are administered and allowed to  
30           reach a particular undesired tissue which is then irradiated with a light absorbed by the

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photoactive compound. This results in destruction or impairment of the surrounding tissue.

Photodynamic therapy of conditions in the eye has been attempted over the past several decades using various photoactive compounds, e.g., porphyrin derivatives, such as hematoporphyrin derivative and Photofrin porfimer sodium; "green porphyrins", such as benzoporphyrin derivative (BPD), MA; and phthalocyanines. Schmidt, U. *et al.* described experiments using BPD coupled with low density lipoprotein (LDL) for the treatment of Greene melanoma (a nonpigmented tumor) implanted into rabbit eyes and achieved necrosis in this context (IOVS (1992) 33:1253 Abstract 2802). This abstract also describes the success of LDL-BPD in achieving thrombosis in a corneal neovascularization model. The corneal tissue is distinct from that of the retina and choroid.

Treatment of choroidal neovascularization using LDL-BPD or liposomal BPD has been reported in IOVS (1993) 34:1303: Schmidt-Erfurth, U. *et al.* (abstract 2956); Haimovici, R. *et al.* (abstract 2955); Walsh, A.W. *et al.* (abstract 2954). Lin, S.C. *et al.* (abstract 2953). An additional publication is Moulton, R.S. *et al.* (abstract 2294), IOVS (1993) 34:1169.

It has now been found that photodynamic treatment of eye conditions unexpectedly enhances the visual acuity of the subject.

20

#### Disclosure of the Invention

The invention is directed to a method to improve visual acuity using photodynamic treatment methods. The methods are particularly effective when the photodynamic therapeutic protocol results in a diminution of unwanted neovasculture, especially neovasculture of the choroid.

25

Accordingly, in one aspect, the invention is directed to a method to enhance visual acuity which comprises administering to a subject in need of such treatment an amount of a formulation of a photoactive compound sufficient to permit an effective amount to localize in the eye of said subject; permitting sufficient time to elapse to

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allow an effective amount of said photoactive compound to localize in said eye; and irradiating the eye with light absorbed by the photoactive compound

#### Brief Description of the Drawings

5        Figure 1 shows preferred forms of the green porphyrins useful in the methods of the invention.

      Figure 2 shows the visual acuity response of individual patients subjected to PDT over time.

10       Figure 3 shows the effect of repeated PDT in individual patients on maintaining enhanced visual acuity.

#### Modes of Carrying Out the Invention

      In the general approach that forms the subject matter of the invention, a human subject whose visual acuity is in need of improvement is administered a suitable  
15       photoactive compound in amount sufficient to provide an effective concentration of the photoactive compound in the eye. After a suitable time period to permit an effective concentration of the compound to accumulate in the desired region of the eye, this region is irradiated with light absorbed by the photoactive compound. The irradiation results in excitation of the compound which, in turn, effects deleterious  
20       effects on the immediately surrounding tissue. The ultimate result is an enhancement of visual acuity in the subject.

#### Photoactive Compounds

      The photodynamic therapy according to the invention can be performed using  
25       any of a number of photoactive compounds. For example, various derivatives of hematoporphyrin have been described, including improvements on hematoporphyrin derivative *per se* such as those described in U.S. Patent Nos. 5,028,621; 4,866,168; 4,649,151; and 5,438,071, the entire contents of which are incorporated herein by reference. In addition, pheophorbides are described in U.S. Patent Nos. 5,198,460;  
30       5,002,962; and 5,093,349; bacteriochlorins in U.S. Patent Nos. 5,171,741 and

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5,173,504; dimers and trimers of hematoporphyrins in U.S. Patent Nos. 4,968,715 and 5,190,966. The contents of these patents are also incorporated herein by reference. In addition, U.S. Patent No. 5,079,262 describes the use of a precursor to hematoporphyrin, aminolevulinic acid (ALA), as the source of a photoactive compound. The use of phthalocyanine photosensitizers in photodynamic therapy is described in U.S. Patent No. 5,166,197. The contents of all of the foregoing patents are incorporated herein by reference. Other possible photoactive compounds include purpurins, merocyanines and porphycenes. Particular preferred photoactive compounds for use in the invention method are the green porphyrins. These porphyrins are described in U.S. Patent Nos. 4,883,790; 4,920,143; 5,095,030; and 5,171,749, the entire contents of which are incorporated herein by reference. As these photoactive agents represent a particularly preferred embodiment, typical formulas for these compounds are represented herein in Figure 1.

Referring to Figure 1, in preferred embodiments each of  $R^1$  and  $R^2$  is independently selected from the group consisting of carbalkoxyl (2-6C), alkyl (1-6C), arylsulfonyl (6-10C), cyano and  $-CONR^3CO$  wherein  $R^3$  is aryl (6-10C) or alkyl (1-6C); each  $R^3$  is independently carboxyl, carboxyalkyl (2-6C) or a salt, amide, ester or acylhydrazone thereof or is alkyl (1-6C);  $R^4$  is  $CH=CH_2$  or  $-CH(OR^4)CH_3$  wherein  $R^4$  is H, or alkyl (1-6C) optionally substituted with a hydrophilic substituent. Especially preferred also are green porphyrins of the formula shown in Figures 1-3 or 1-4 or mixtures thereof.

More preferred are embodiments are those wherein the green porphyrin is of the formula shown in Figure 1-3 or 1-4 or a mixture thereof and wherein each of  $R^1$  and  $R^2$  is independently carbalkoxyl (2-6C); one  $R^3$  is carboxyalkyl (2-6C) and the other  $R^3$  is an ester of a carboxyalkyl (2-6C) substituent; and  $R^4$  is  $CH=CH_2$  or  $-CH(OH)CH_3$ .

Still more preferred are embodiments wherein green porphyrin is of the formula shown in Figure 1-3 and wherein  $R^1$  and  $R^2$  are methoxycarbonyl; one  $R^3$  is  $-CH_2CH_2COOCH_3$  and the other  $R^3$  is  $CH_2CH_2COOH$ ; and  $R^4$  is  $CH=CH_2$ ; i.e., BPD-MA.

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Any of the photoactive compounds described above can be used in the method of the invention; of course, mixtures of two or more photoactive compounds can also be used; however, the effectiveness of the treatment depends on the absorption of light by the photoactive compound so that if mixtures are used, components with similar  
5 absorption maxima are preferred.

### Formulations

The photoactive agent is formulated so as to provide an effective concentration to the target ocular tissue. The photoactive agent may be coupled to a specific binding  
10 ligand which may bind to a specific surface component of the target ocular tissue or, if desired, by formulation with a carrier that delivers higher concentrations to the target tissue.

The nature of the formulation will depend in part on the mode of administration and on the nature of the photoactive agent selected. Any pharmaceutically acceptable  
15 excipient, or combination thereof, appropriate to the particular photoactive compound may be used. Thus, the photoactive compound may be administered as an aqueous composition, as a transmucosal or transdermal composition, or in an oral formulation. The formulation may also include liposomes. Liposomal compositions are particularly preferred especially where the photoactive agent is a green porphyrin. Liposomal  
20 formulations are believed to deliver the green porphyrin selectively to the low-density lipoprotein component of plasma which, in turn acts as a carrier to deliver the active ingredient more effectively to the desired site. Increased numbers of LDL receptors have been shown to be associated with neovascularization, and by increasing the partitioning of the green porphyrin into the lipoprotein phase of the blood, it appears to  
25 be delivered more efficiently to neovasculture.

As previously mentioned, the method of the invention is particularly effective where the loss of visual acuity in the patient is associated with unwanted neovasculture. Green porphyrins, and in particular BPD-MA, strongly interact with such lipoproteins. LDL itself can be used as a carrier, but LDL is considerably more  
30 expensive and less practical than a liposomal formulation. LDL, or preferably

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liposomes, are thus preferred carriers for the green porphyrins since green porphyrins strongly interact with lipoproteins and are easily packaged in liposomes. Compositions of green porphyrins involving lipocomplexes, including liposomes, are described in U.S. Patent 5,214,036 and in U.S. Serial No. 07/832,542 filed 5 February 1992, the  
5 disclosures of both of these being incorporated herein by reference. Liposomal BPD-MA for intravenous administration can also be obtained from QLT PhotoTherapeutics Inc., Vancouver, British Columbia.

#### Administration and Dosage

10 The photoactive compound can be administered in any of a wide variety of ways, for example, orally, parenterally, or rectally, or the compound may be placed directly in the eye. Parenteral administration, such as intravenous, intramuscular, or subcutaneous, is preferred. Intravenous injection is especially preferred.

The dose of photoactive compound can vary widely depending on the mode of  
15 administration; the formulation in which it is carried, such as in the form of liposomes; or whether it is coupled to a target-specific ligand, such as an antibody or an immunologically active fragment. As is generally recognized, there is a nexus between the type of photoactive agent, the formulation, the mode of administration, and the dosage level. Adjustment of these parameters to fit a particular combination is  
20 possible.

While various photoactive compounds require different dosage ranges, if green porphyrins are used, a typical dosage is of the range of 0.1-50 mg/M<sup>2</sup> (of body surface area) preferably from about 1-10 mg/M<sup>2</sup> and even more preferably about 2-8 mg/M<sup>2</sup>.

The various parameters used for effective, selective photodynamic therapy in  
25 the invention are interrelated. Therefore, the dose should also be adjusted with respect to other parameters, for example, fluence, irradiance, duration of the light used in photodynamic therapy, and time interval between administration of the dose and the therapeutic irradiation. All of these parameters should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue.



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Stated in alternative terms, as the photoactive compound dose is reduced, the fluence required to close choroidal neovascular tissue tends to increase.

#### Light Treatment

5       After the photoactive compound has been administered, the target ocular tissue is irradiated at the wavelength absorbed by the agent selected. The spectra for the photoactive compounds described above are known in the art; for any particular photoactive compound, it is a trivial matter to ascertain the spectrum. For green porphyrins, however, the desired wavelength range is generally between about 550 and  
10   695 nm. A wavelength in this range is especially preferred for enhanced penetration into bodily tissues.

As a result of being irradiated, the photoactive compound in its excited state is thought to interact with other compounds to form reactive intermediates, such as singlet oxygen, which can cause disruption of cellular structures. Possible cellular  
15   targets include the cell membrane, mitochondria, lysosomal membranes, and the nucleus. Evidence from tumor and neovascular models indicates that occlusion of the vasculature is a major mechanism of photodynamic therapy, which occurs by damage to endothelial cells, with subsequent platelet adhesion, degranulation, and thrombus formation.

20       The fluence during the irradiating treatment can vary widely, depending on type of tissue, depth of target tissue, and the amount of overlying fluid or blood, but preferably varies from about 50-200 Joules/cm<sup>2</sup>.

The irradiance typically varies from about 150-900 mW/cm<sup>2</sup>, with the range between about 150-600 mW/cm<sup>2</sup> being preferred. However, the use of higher  
25   irradiances may be selected as effective and having the advantage of shortening treatment times.

The optimum time following photoactive agent administration until light treatment can also vary widely depending on the mode of administration, the form of administration and the specific ocular tissue being targeted. Typical times after

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administration of the photoactive agent range from about 1 minute to about 2 hours, preferably about 5-30 minutes, and more preferably 10-25 minutes.

The duration of light irradiation depends on the fluence desired; for an irradiance of 600 mW/cm<sup>2</sup> a fluence of 50 J/cm<sup>2</sup> requires 90 seconds of irradiation; 150 J/cm<sup>2</sup> requires 270 seconds of irradiation.

#### Evaluation of Treatment

Clinical examination and fundus photography typically reveal no color change immediately following photodynamic therapy, although a mild retinal whitening occurs in some cases after about 24 hours. Closure of choroidal neovascularization is preferably confirmed histologically by the observation of damage to endothelial cells. Observations to detect vacuolated cytoplasm and abnormal nuclei associated with disruption of neovascular tissue may also be evaluated.

In general, effects of the photodynamic therapy as regards reduction of neovascularization can be performed using standard fluorescein angiographic techniques at specified periods after treatment.

Of paramount importance with respect to the present invention is the evaluation of visual acuity. This is done using means standard in the art and conventional "eye charts" in which visual acuity is evaluated by the ability to discern letters of a certain size, usually with five letters on a line of given size. Measures of visual acuity are known in the art and standard means are used to evaluate visual acuity according to the present invention.

The following examples are to illustrate but not to limit the invention.

#### Example 1

##### Comparison of Various PDT Regimens

Groups of patients who had been diagnosed as qualified for experimental treatment of age-related macular degeneration (AMD) were divided into three groups.

Group A, of 22 patients, was treated with a regimen in which they were administered 6 mg/M<sup>2</sup> (of body surface area) of BPD-MA in the commercially available liposomal intravenous composition obtainable from QLT PhotoTherapeutics, Vancouver, BC. Administration was intravenous. Thirty minutes after the start of infusion, these patients were administered irradiance of 600 mW/cm<sup>2</sup> and total fluence of either 50 J/cm<sup>2</sup>, 75 J/cm<sup>2</sup>, 100 J/cm<sup>2</sup>, 105 J/cm<sup>2</sup> or 150 J/cm<sup>2</sup> of light from a coherent Argon dye laser No. 920, Coherent Medical Laser, Palo Alto, CA (Ohkuma, H. *et al. Arch Ophthalmol* (1983) 101:1102-1110; Ryan, S.J., *Arch Ophthalmol* (1982) 100:1804-1809).

10 A second group of 15 patients, Group B, was also administered 6 mg/M<sup>2</sup> BPD-MA in the liposomal formulation, intravenously as in Group A, but irradiation, conducted as described for Group A, began 20 minutes after the start of infusion.

The 15 patients in Group C were subjected to a regime identical to those in Group A except that the BPD-MA was administered at 12 mg/M<sup>2</sup>

15 To evaluate the patients after treatment, fluorescein angiography was performed 1 week, 4 weeks and 12 weeks after treatment. Visual acuity tests using standard eye charts were administered 3 months after treatment. The change in visual acuity was averaged for each group regardless of the total fluence of light administered.

20 After 3 months, patients subjected to regimen A showed an improvement in visual acuity of +0.10 (an improvement of 1.0 would indicate an improvement of one line on the conventional eye charts). Patients subjected to regimen B showed an enhancement of visual acuity of +0.53; those on regimen C decreased in visual acuity at an average of -0.40.

25 By comparison, 184 patients treated using standard photocoagulation treatment as described by a Macular Photocoagulation Study Group in *Clinical Sciences* (1991) 109:1220-1231, showed a diminution in visual acuity 3 months after treatment of -3.0. This was worse than the results of no treatment where a sample of 179 patients suffering from AMD showed a loss of visual acuity over this time period of -2.0.

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Thus, it appeared that regimen B wherein 6 mg/M<sup>2</sup> of BPD in a liposomal formulation were administered and irradiation began 20 minutes later was the best of these three protocols tested.

5

### Example 2

#### Time Course of Enhancement of Visual Acuity

Sixteen patients in the study were subjected to regimen B described in Example 1 above and evaluated for visual acuity after 1 week and after 4 weeks as well as after 3 months. One week after treatment these patients had an average increase in visual  
10 acuity of +2.13; 4 weeks after treatment the average was +1.25 and after 3 months, +0.53.

These results seemed at least partly to correlate with success in closing choroidal neovascularity (CNV). For those patients in regimen B, 10 of the 16 tested by fluorescein angiography showed CNV more than 50% closed after 4 weeks with a  
15 corresponding increase in visual acuity of +1.6. The remaining 6 patients who showed less than 50% closure of CNV after 4 weeks showed an enhanced visual acuity of +0.7.

Of 15 patients subjected to regimen C of Example 1, 7 showed more than 50% closure of CNV and an enhanced visual acuity of +1.4. Three of the 15 showed less  
20 than 50% closure of CNV and showed a loss of visual acuity of -0.3. Five of the 15 showed classic CNV recurrence and showed a loss of visual acuity of -1.6.

On the other hand, after 4 weeks of treatment with regimen A, 9 of 21 patients showed a CNV of more than 50% closure but a decline in visual acuity of -0.2. Nine  
25 of the 21 showed a closure of CNV of less than 50% and an enhanced visual acuity of +0.9. Three of the 21 patients treated who showed classic CNV recurrence showed no change in visual acuity.

After 3 months, the results are as shown in Table 1, where the change in visual acuity observed is noted.

Table 1			
	Regimen A	Regimen B	Regimen C
Classic CNV $\geq$ 50% closed	+0.7 (3/20)	+3 (4/13)	- (0/12)
Classic CNV < 50% closed	+0.14 (7/20)	0 (3/13)	+1.75 (4/12)
Classic CNV Recurrence	-0.1 (10/20)	-0.3 (6/13)	-1.4 (8/12)

Thus, there appears to be some, but far from perfect correlation between CNV closure and enhancement of visual acuity. The method of the invention may thus be most readily applied to patients showing unwanted neovasculation, especially in the choroid. Thus, suitable indications would include macular degeneration, ocular histoplasmosis syndrome, myopia, and inflammatory diseases.

Figure 2 shows a graphic representation of the time course of change in visual acuity of individual patients subjected to regimen B. All patients showed improvement, although in some cases the improvement diminished over time after treatment.

### Example 3

#### Effect of Iterative Treatment

Individual patients were treated with regimen B as described in Example 1 and then retreated at 2 and 6 weeks from the initial treatment. Repeating the treatment appeared to enhance the degree of increased visual acuity. The results are summarized in Figure 3.

As shown in Figure 3, for example, patient no. 901 starting at a base line of 20/126 showed an enhancement of +2 in visual acuity after week 2; two weeks after a second treatment, the enhancement was +5 over base line. For patient 906, the enhancement after the first treatment at week 2 was +2; this increased to +3 one week after a second treatment. While some patients showed slight relapses, in general, repeating the regimen maintained or increased enhancement of visual acuity.

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Claims

1. A method to improve visual acuity in a human subject, which method comprises:
  - 5 a) administering to a subject in need of such treatment an amount of a formulation of a photoactive compound sufficient to permit an effective amount to localize in the eye of said subject;
  - b) permitting sufficient time to elapse to allow an effective amount of said photoactive compound to localize in said eye; and
  - 10 c) irradiating the eye with light absorbed by the photoactive compound.
2. The method of claim 1 wherein the eye of said subject contains unwanted neovasculation.
- 15 3. The method of claim 2 wherein the neovasculation is choroidal neovasculation.
4. The method of claim 1 wherein the photoactive agent is a green porphyrin, a hematoporphyrin derivative, a chlorin, or a phlorin.
- 20 5. The method of claim 4 wherein said photoactive compound is a green porphyrin.
- 25 6. The method of claim 5 wherein said green porphyrin is Formula 1-3 or 1-4 of Figure 1  
wherein each of  $R^1$  and  $R^2$  is independently selected from the group consisting of carbalkoxyl (2-6C), alkyl (1-6C), arylsulfonyl (6-10C), cyano and  $-CONR^3CO$  wherein  $R^3$  is aryl (6-10C) or alkyl (1-6C);

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each  $R^3$  is independently carboxyl, carboxyalkyl (2-6C) or a salt, amide, ester or acyl hydrazone thereof, or is alkyl (1-6C);

$R^4$  is  $\text{CH}=\text{CH}_2$  or  $-\text{CH}(\text{OR}^4)\text{CH}_3$  wherein  $R^4$  is H, or alkyl (1-6C) optionally substituted with a hydrophilic substituent.

5

7. The method of claim 6 wherein said green porphyrin is of the formula shown in Figures 1-3 or 1-4 of Figure 1 wherein each of  $R^1$  and  $R^2$  is independently carbalkoxyl (2-6C);

one  $R^3$  is carboxyalkyl (2-6C) and the other  $R^3$  is the ester of a carboxyalkyl (2-6C) substituent; and

10

$R^4$  is  $\text{CH}=\text{CH}_2$  or  $-\text{CH}(\text{OH})\text{CH}_3$ .

8. The method of claim 7 wherein said green porphyrin is of the formula shown in Figure 1-3 and

15

wherein  $R^1$  and  $R^2$  are methoxycarbonyl;

one  $R^3$  is  $-\text{CH}_2\text{CH}_2\text{COOCH}_3$  and the other  $R^3$  is  $\text{CH}_2\text{CH}_2\text{COOH}$ ; and

$R^4$  is  $\text{CH}=\text{CH}_2$  i.e., BPD-MA.

9. The method of claim 1 wherein said formulation contains said photoactive agent complexed with low-density lipoprotein.

20

10. The method of claim 1 wherein said formulation is a liposomal preparation.

11. The method of claim 1 wherein said subject has been diagnosed with age-related macular degeneration (AMD).

25

12. The method of claim 1 wherein steps a), b) and c) are repeated at least once.

30

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13. The method of claim 1 wherein the subject has been diagnosed with a condition selected from the group consisting of macular degeneration, ocular histoplasmosis syndrome, myopia, and inflammatory diseases.



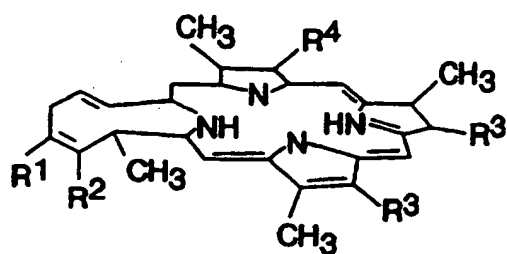


FIG. 1A

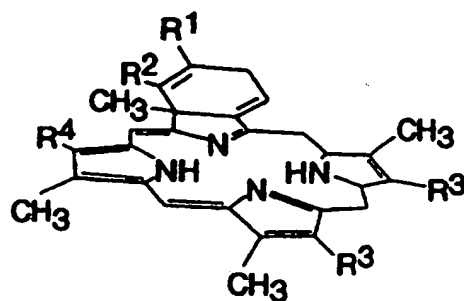


FIG. 1B

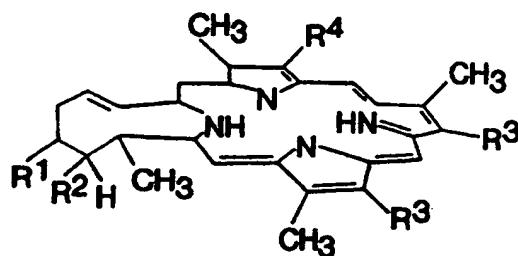


FIG. 1C

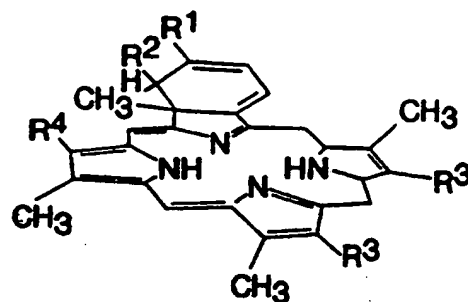


FIG. 1D

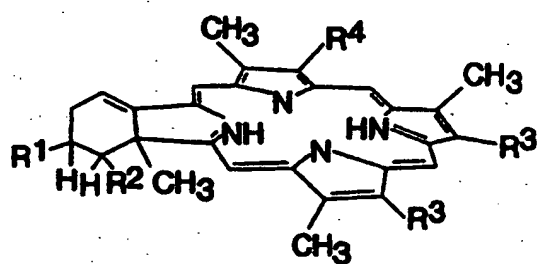


FIG. 1E

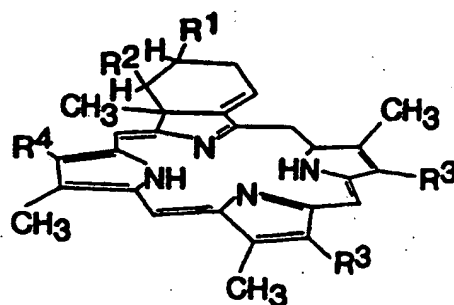


FIG. 1F

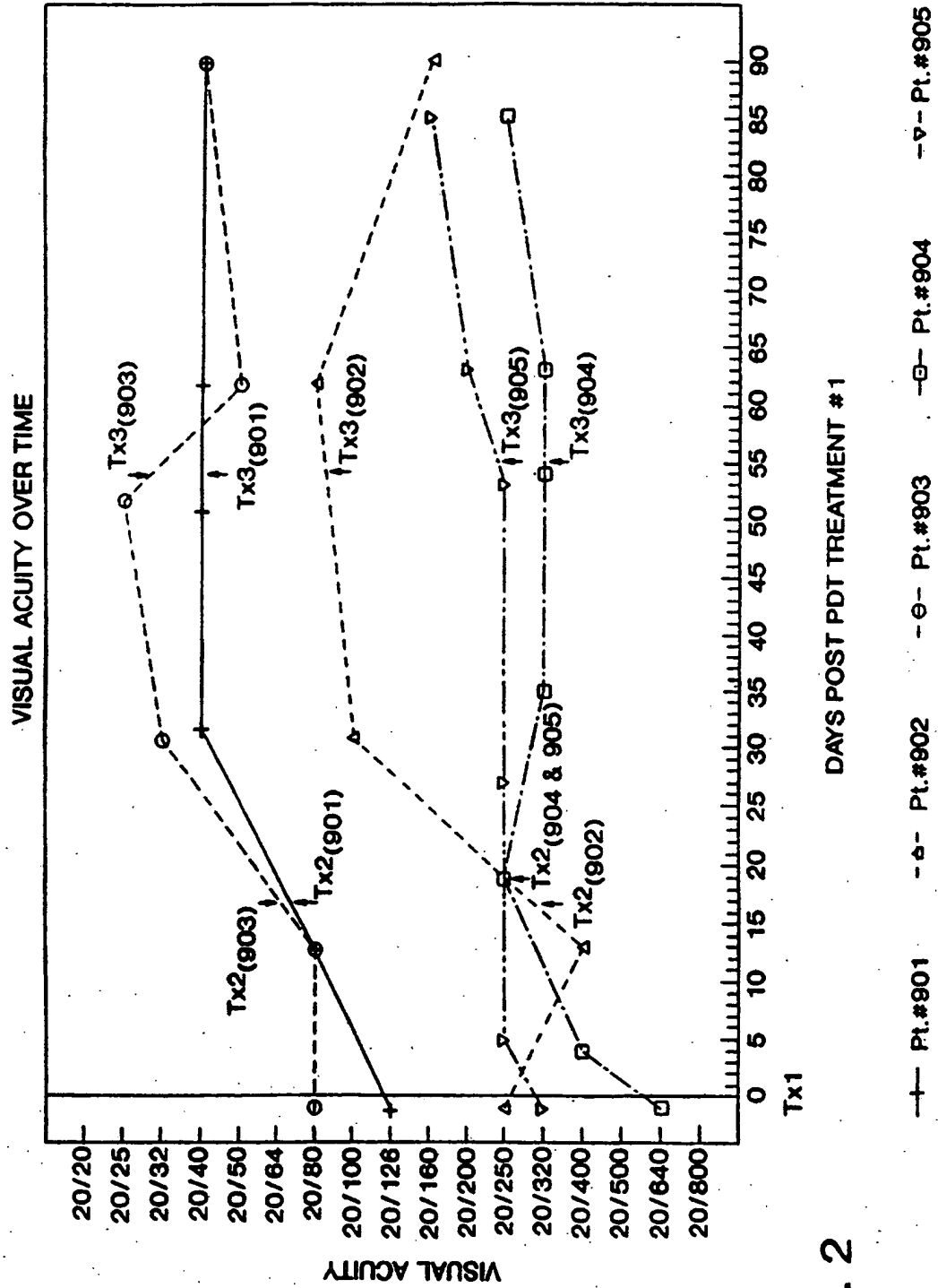


FIG. 2

VISUAL ACUITY  
RETREATMENTS AT 2 AND 6 WEEKS  
SNELLEN EQUIVALENT (LINES CHANGED FROM BASELINE)

Patient No.	Baseline	T1W1	T1W2	T1W3	T2W1	T2W2	T2W4	T3W1	T3W4
901	20/126		20/80 (+2)			20/40 (+5)	20/40 (+5)	20/40 (+5)	20/40 (+5)
902	20/250		20/400 (-2)			20/100 (+4)		20/80 (+5)	20/160 (+2)
903	20/80		20/80 (0)			20/32 (+3)	20/25 (+4)	20/50 (+2)	20/40 (+3)
904	20/640	20/400 (+2)	20/250 (+4)			20/320 (+3)	20/320 (+3)	20/320 (+3)	20/250 (+4)
905	20/320	20/250 (+1)		20/250 (+1)	20/250 (+1)		20/250 (+1)	20/200 (+2)	20/160 (+3)
906	20/200		20/126 (+2)		20/100 (+3)			20/100 (+3)	
907	20/200	20/126 (+2)			20/100 (+3)				
908	20/200	20/126 (+2)			20/50 (+4)				
909	20/320	20/160 (+3)			20/160 (+3)				
910	20/100	20/100 (0)			20/126 (-1)				

T = PDT TREATMENT #

W = WEEKS AFTER TREATMENT

FIG. 3

# INTERNATIONAL SEARCH REPORT

Inter- national Application No  
PCT/CA 97/00134

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61K41/00 A61K31/40		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF CLINICAL LASER MEDICINE & SURGERY, vol. 15, no. 1, February 1997, page 48 XP000672382 "QTL PHOTOTHERAPEUTICS ENTERS PHASE III TRIAL FOR AGE-RELATED MACULAR DEGENERATION" see the whole document ---	1-8, 11-13
X	INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 37, no. 3, 15 February 1996, page 580 XP002032185 U. SCHMIDT-ERFURTH ET AL.: "PHOTODYNAMIC THERAPY OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION USING BENZOPORPHYRIN DERIVATIVE: FIRST RESULTS OF A MULTI-CENTER TRIAL" see the whole document --- -/-	1-13
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to underpin the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center;">3 June 1997</div>		Date of mailing of the international search report  <div style="text-align: center;">20.06.1997</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tlx. 31 651 epo nl, Fax (+ 31-70) 340-3016		Authorized officer  <div style="text-align: center;">Hoff, P</div>

# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/CA 97/00134

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>INVESTIGATIVE OPHTHALMOLOGY &amp; VISUAL SCIENCE, vol. 37, no. 3, 15 February 1996, page 5223 XP002032186 A. BUNSE ET AL.: "PHOTODYNAMIC THERAPY OF CHOROIDAL NEOVASCULARIZATION: EFFECTS ON RETINAL FUNCTION DOCUMENTED BY MICROPERIMETRY" see the whole document ---</p>	1-13
X	<p>WO 95 24930 A (MASSACHUSETTS EYE &amp; EAR INFIRM) 21 September 1995 see the whole document ---</p>	1-13
X	<p>ARCHIVES OF OPHTHALMOLOGY, vol. 113, no. 6, 1995, pages 810-818, XP000672344 J.W. MILLER ET AL.: "PHOTODYNAMIC THERAPY OF EXPERIMENTAL CHOROIDAL NEOVASCULARIZATION USING LIPOPROTEIN-DELIVERED BENZOPORPHYRIN" see the whole document ---</p>	1-13
A	<p>ARCHIVES OF OPHTHALMOLOGY, vol. 114, no. 2, February 1996, pages 186-192, XP000672345 L.H.Y. YOUNG ET AL.: "PHOTODYNAMIC THERAPY OF PIGMENTED CHOROIDAL MELANOMAS USING A LIPOSOMAL PREPARATION OF BENZOPORPHYRIN DERIVATIVE" see the whole document -----</p>	1-13

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 97/ 00134

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-13  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-13  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

**information on patent family members**

Internal Application No

PC1/CA 97/00134

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524930 A	21-09-95	AU 6813694 A	03-10-95